

Chapter 7

Pharmaceutical Suspensions



Anteneh Belayneh

(B. Pharm, MSc in Pharmaceuticals)

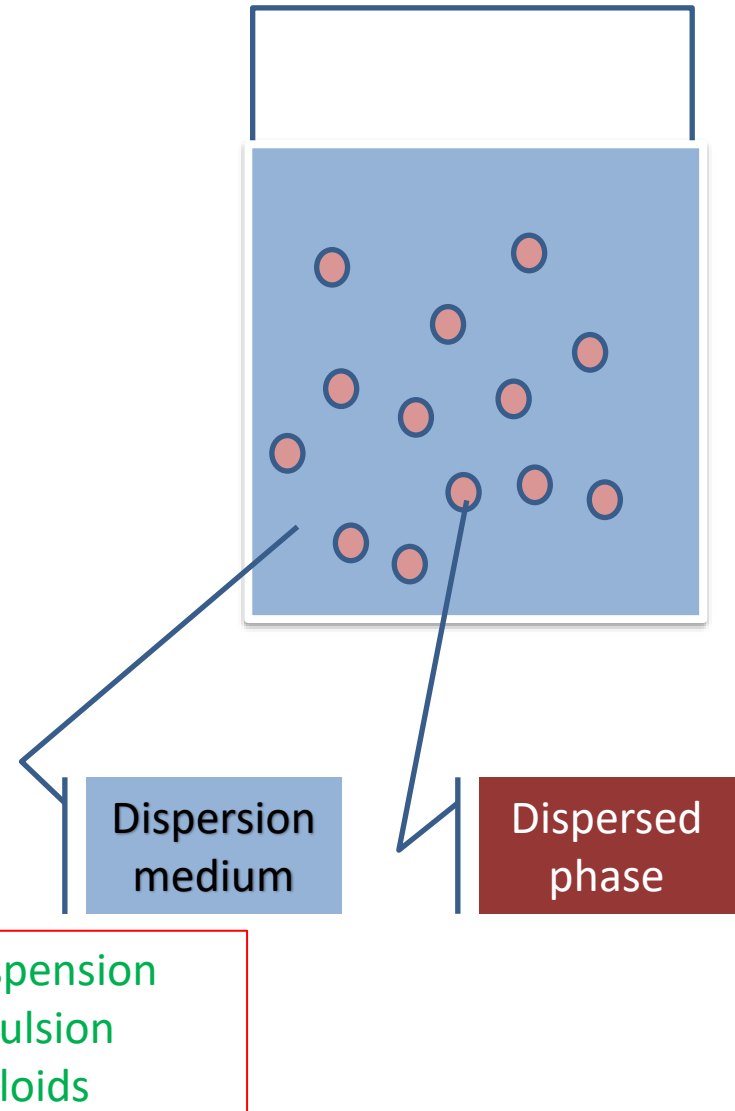
Pharmaceutical Suspensions

Outline

- Introduction
- Desirable properties
- Classification
- Interfacial properties
- Sedimentation
- Ingredients
- Formulation approaches
- Rheology
- Preparation
- Labeling and storage

Dispersed system

- Dispersed systems
 - Are systems which consist of:
 - Particulate matter (***dispersed phase***)
 - It is the component present ***in small*** proportion and is just like a solute in a solution
 - Dispersion medium (***continuous phase***)
 - A component present ***in excess*** and is just like a solvent in a solution



Pharmaceutical Suspensions

Introduction

- Suspensions are preparations containing:
 - finely divided drug particles (the *suspensoid*) distributed somewhat uniformly throughout a vehicle in which the drug exhibits a minimum degree of solubility.

Suspensoid = dispersed phase = internal phase

Vehicle = dispersion medium = external or continuous phase

- may be presented as:
 - ready to-use form, or
 - dry powders for suspension (reconstitution)
 - E.g. many antibiotic drugs (“for Oral Suspension”)

Pharmaceutical Suspensions

Introduction...

- Depending on particle size of dispersed phase:
 - Coarse dispersions (10–50 μm): suspensions and emulsions
 - Fine dispersions (0.5–10 μm): Magmas and gels
 - Colloidal dispersions (1.0 nm and 0.5 μm)

Suspensions can be administered through d/t routes:

✓ oral, parental, ophthalmic, aerosol, and topical...

Pharmaceutical Suspensions

Introduction...

Reasons

- Easier administration: some patients have difficulty of swallowing
- Stability: certain drugs are chemically unstable in solution but stable when suspended.
- Palatability: disagreeable taste of certain drugs in solution form is overcome when the drug is administered as an oral suspension.

E.g. Erythromycin estolate, Chloramphenicol palmitate

- Higher bioavailability:
 - Solution > Suspension > Capsule > Compressed Tablet > Coated tablet

Pharmaceutical Suspensions

Introduction...

Limitations

- Physical instability: sedimentation can cause problems.
- It is bulky: sufficient care must be taken during handling and transport.
- It is difficult to formulate
- Uniform and accurate dose can not be achieved unless suspensions are packed in unit dosage form.

Pharmaceutical Suspensions

Desirable properties

○ An ideal suspension:

- Should settle slowly and should be readily redispersed upon gentle shaking of the container.
 - the particle size of the suspensoid should remain fairly constant throughout long periods of undisturbed standing.
 - physically, chemically, and biologically stable
 - the suspension should pour readily and evenly from its container.
- ✓ These properties depend on the nature of the **dispersed phase, the dispersion medium, and pharmaceutical adjuncts.**

Pharmaceutical Suspensions

Classification

○ **Based on route of administration**

- Oral suspension: e.g. Paracetamol suspension, antacids
- Externally applied suspension: e.g. Calamine lotion
- Parenteral suspension: e.g. Penicillin G Benzathine, Insulin Zinc Suspension

○ **Based on proportion of solid particles**

- Dilute suspension (2 to 10% w/v solid): e.g. cortisone acetate
- Concentrated suspension (up to 50% w/v solid): e.g. zinc oxide suspension

Pharmaceutical Suspensions

Classification...

- **Based on the ease of suspendability:**

- i. Diffusible suspensions

- ✓ Contain light powders (insoluble, or only very slightly soluble) but after shaking **disperse evenly** throughout the vehicle for **long enough**

- Examples:

- ✓ Light Kaolin BP (insoluble in water)

- ✓ Light Magnesium Carbonate BP (very slightly soluble)

- ✓ Magnesium Trisilicate BP (insoluble)

Pharmaceutical Suspensions

Classification...

- **Based on the ease of suspendability:**

- ii. In-diffusible suspensions

- ✓ contain heavy powders that are insoluble in the vehicle and on shaking do not disperse evenly throughout the vehicle long enough.

Examples: Aspirin BP, Calamine BP, Zinc Oxide BP

Pharmaceutical Suspensions

Classification...

○ **Based on size of solid particles**

- Coarse suspensions: suspended particle sizes of 1 to 100 μm
- Colloidal suspensions: suspended particle sizes of 1 nm to 1 μm .
- Nano suspensions: suspended particle sizes of < 1 nm

○ **Based on Electrokinetic Nature of solid particles**

- Flocculated suspension
- Deflocculated suspension

Pharmaceutical Suspensions

Interfacial properties

Zeta potential, or ζ

- Zeta potential is a measure of the magnitude of the electrostatic or charge repulsion/attraction between particles and is one of the fundamental parameters known to affect stability.
- Its measurement brings detailed insight into the causes of dispersion, aggregation or flocculation, and can be applied to improve the formulation of dispersions, emulsions and suspensions.
 - shows magnitude of repulsive forces.

Pharmaceutical Suspensions

Interfacial properties

Zeta potential, or ζ

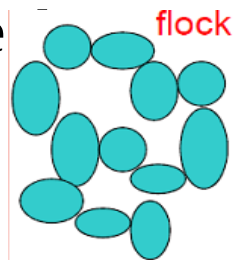
- if the zeta potential is reduced below a certain value, the attractive forces exceed the repulsive forces, and the particles come together.
 - ✓ this phenomenon is known as **flocculation** (opposite is deflocculation).
 - ✓ the system is flocculated (the opposite is deflocculated).
- Thus the phenomenon of flocculation and deflocculation **depends** on zeta potential carried by particles.

Pharmaceutical Suspensions

Interfacial properties...

Flocculated systems

- In flocculated suspensions,
 - zeta potential is lower than critical values.
 - The weak Vander Waals force greater than the attraction force
 - ✓ as a result the attractive forces $>$ repulsive forces
 - ✓ this leads to flocculation (formation of flocs (loose aggregates)). (between distance 10-20nm)
 - the formed flocs will cause increase in sedimentation rate increase in size of sedimenting particles.
 - hence, flocculated suspensions sediment more rapidly.



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Interfacial properties...

Deflocculated systems

- In deflocculated suspensions,
 - zeta potential is higher than critical value (25mV) so that the repulsive forces dominate the attractive forces.
 - particles remain suspended for a long period of time, and only a small portion of the solid is found in the sediment due to the force of gravity.
 - individual particles are settling.
 - Sedimentation height is very low
 - rate of sedimentation is slow, which prevents entrapping of liquid medium which makes it difficult to re-disperse by agitation.
- ✓ this phenomenon is called ‘caking’ or ‘claying’.



Pharmaceutical Suspensions

Interfacial properties...

Flocculated	Deflocculated
1. Particles form loose aggregates and form a network like structure 2. Rate of sedimentation is high 3. Sediment is rapidly formed 4. Sediment is loosely packed and doesn't form a hard cake 5. Sediment is easy to redisperse 6. Suspension is not pleasing in appearance 7. The floccules stick to the sides of the bottle	1. Particles exist as separate entities 2. Rate of sedimentation is slow 3. Sediment is slowly formed 4. Sediment is very closely packed and a hard cake is formed 5. Sediment is difficult to redisperse 6. Suspension is pleasing in appearance 7. They don't stick to the sides of the bottle

Pharmaceutical Suspensions

Sedimentation parameters

Sedimentation rate

- The various factors involved in the rate of settling of the particles of a suspension are embodied in the equation of **Stokes law**.

$$\frac{dx}{dt} = \frac{d^2(\rho_i - \rho_e)g}{18\eta}$$

Where,

- dx/dt is the rate of settling
- d is the diameter of the particles
- ρ_i is the density of the particle
- ρ_e is the density of the medium
- g is the gravitational constant, and
- η is the viscosity of the medium

Pharmaceutical Suspensions

Sedimentation...

Sedimentation rate...

- **Factors** to be adjusted to enhance the physical stability of a suspension:
 - Particle size: a decrease in particle size by a factor of 10 results in a reduction in the rate of settling by a factor of 100.
 - density and viscosity of the medium:
 - ✓ using other vehicles (e.g. glycerin: $\eta = 400$ cP; $\rho = 1.25$ g/mL)
 - ✓ adding viscosity enhancers

Limitations of Stock's law:

- particles are uniform, perfectly spherical in a very dilute conc.
- no turbulence, collision with other particles, and
- no chemical or physical attraction or affinity for the dispersion medium

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Sedimentation...

Sedimentation volume

- is the ratio of the equilibrium volume of the sediment, V_u , to the total volume of the suspension, V_o

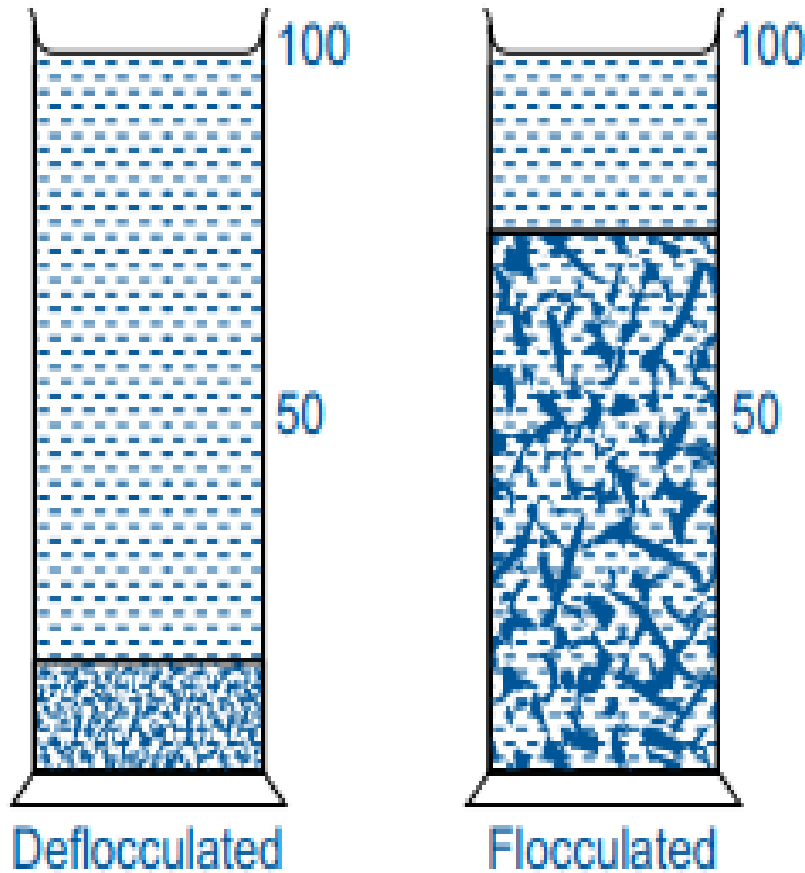
$$F = \frac{V_u}{V_o} = \frac{H_u}{H_o}$$

- F has values ranging from less than one to greater than one.
- When $V_u < V_o$ $F < 1$
 - When $V_u = V_o$, $F = 1$, flocculation equilibrium, shows no sedimentation (no clear supernatant on standing).

Pharmaceutical Suspensions

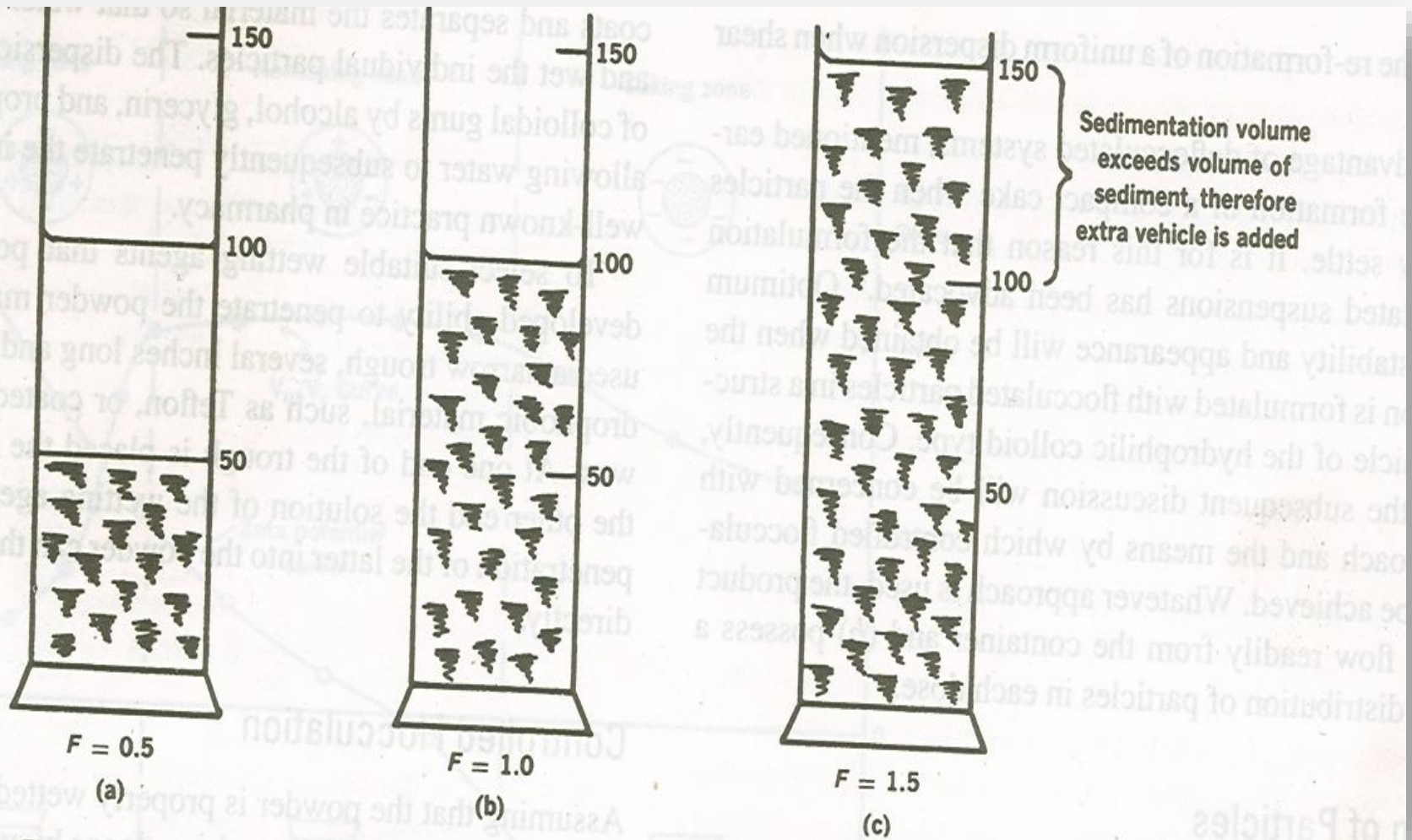
Sedimentation...

Sedimentation volume...



Deflocculated suspension: $F_{\infty} = 0.15$; Flocculated suspension: $F = 0.75$; $\beta = 5.0$.

- When $V_u > V_o$, $F > 1$
 - Sediment volume is greater than the original volume due to the network of flocs formed in the suspension is so loose and fluffy that the volume they encompass is greater than the original volume of the suspension.
 - needs extra vehicle to contain the sediment when $F > 1$
- ***Sedimentation volume*** gives only qualitative account of flocculation and lacks a meaningful reference point



Pharmaceutical Suspensions

Sedimentation...

Degree of flocculation

- *degree of flocculation*, β , is a better parameter for comparing flocculated systems.
- it relates the sedimentation volume of the flocculated suspension, F , to the sedimentation volume of the suspension when deflocculated, F_{∞} .

$$\beta = \frac{F_u}{F_{\infty}}$$

- shows the increased sediment volume resulting from flocculation.
 - if, for example, β has a value of 5.0
 - the minimum value of β is 1, when flocculated suspension sedimentation volume is equal to the sedimentation volume of deflocculated suspension.
- formulations with larger values of β are selected if the aim is to produce as flocculated a product as possible.

Example 1:

Determine the sedimentation volume of a 2.5% w/v suspension of paracetamol in water. The initial volume of the suspension was 100 mL while the final volume of the sediment was found to be 44 mL. If the degree of flocculation is 1.5, what is the deflocculated sedimentation volume?

Example 2:

A 200 mL of suspension of a drug in water was made and the final volume of the sediment was found to be 60 mL. Calculate the sedimentation volume and deflocculated sedimentation volume if the degree of flocculation is found to be 1.3.

Pharmaceutical Suspensions

Ingredients

- **Suspending agent:** form colloidal dispersion with water and increase the viscosity of the continuous phase.
 - Preferred suspending agents are those that give thixotropy to the media such as Xanthan gum, Carageenan, Na CMC.
- **Wetting agent** (surfactants; HLB value of 7-9): increase wettability
 - alcohol, glycerin, and propylene glycol may be used sometimes in the initial stages to disperse
- **Buffers:** control the pH: acetate, phosphate, citrate, carbonate
- **Osmotic agents:** added to render osmotic pressure comparable to biological fluids: NaCl, mannitol, dextrose

Pharmaceutical Suspensions

Ingredients...

- **Preservatives:** to prevent microbial contamination: Benzalkonium chloride, Benzoic acid, Butyl paraben
- **Flavoring and coloring agents:** added to increase patient acceptance: Anise oil, Thyme oil, Titanium dioxide (white), Brilliant blue (blue), Indigo carmine (blue), Amaranth (red)
- **Sweetening Agents:** sucrose, sorbitol, sodium saccharin, Aspartame
- **Humectants:** prevent evaporation of water: propylene glycol, glycerol
- **Antioxidant:** prevent oxidation: ascorbic acid, Sodium bisulfite, BHT, BHA

Pharmaceutical Suspensions

Formulation approaches

- Three approaches: depending on whether the suspension is flocculated or deflocculated.
 - ✓ Using structured vehicle
 - ✓ Controlled flocculation
 - ✓ Combination of both of the methods

Pharmaceutical Suspensions

Formulation approaches...

Structured vehicles

- are also called thickening or suspending agents.
- are aqueous solutions of natural and synthetic polymers
- are used to increase the viscosity of the suspension.
- they entrap and reduce the sedimentation of suspended particles.

E.g. methyl cellulose, sodium carboxy methyl cellulose, acacia, gelatin and tragacanth, bentonite, carbomer

Caution: too much viscosity is not required as it causes:

- Difficulty of shaking
- difficulty in pouring and administration.
- may affect drug absorption since they adsorb on the surface of particle and suppress the dissolution rate.

Pharmaceutical Suspensions

Formulation approaches... Controlled flocculation

- Controlled flocculation of particles is obtained by adding flocculating agents:
 - Electrolytes: are probably the most widely used flocculating agents.
 - ✓ act by reducing the electrical forces of repulsion between particles, thereby allowing the particles to form the loose flocs.
 - ✓ Cationic (for organic substances) or anionic electrolytes (for minerals)
 - Surfactants: Ionic detergents can produce flocculation by neutralization of the charges on the surface of the drug particle.
 - Polymers: generally less well understood than flocculation by electrolytes
 - ✓ their successful use as flocculants may require trial and error in order to identify optimal selection of a polymer and an appropriate concentration.

Pharmaceutical Suspensions

Formulation approaches...

Flocculation in structured vehicles

- Sometimes suspending agents can be added to flocculated suspension to retard sedimentation (if F is not close or equal to 1).
- Examples of these agents are: Carboxymethylcellulose (CMC), Carbopol, Veegum, tragacanth, and bentonite have been employed, either alone or in combination.
- all the structured vehicles in common use are hydrophilic colloids.
 - ✓ incompatibility may arise with the flocculating agent if the charge on the particles is originally negative.
 - ✓ the negatively charged suspending agent may coagulate and lose its suspendability.

Pharmaceutical Suspensions

Formulation approaches...

Particles

Addition of wetting agent and dispersion medium

Uniform dispersion of deflocculated particles

Addition of structured vehicle

Deflocculated suspension in structured vehicle as a final product

Addition of flocculating agent

Flocculated suspension as a final product

Addition of flocculating agent

Flocculated suspension

Addition of structured vehicle

Flocculated suspension in structured vehicle as a final product

Alternative approaches to the formulation of suspensions

Pharmaceutical Suspensions

Preparation

- Small scale preparation of suspensions:

Step 1:

- the insoluble materials are ground (or) levigated in the mortar to a smooth paste with a vehicle containing the wetting agent.



Step 2:

- all soluble ingredients are dissolved in same portion of the vehicle and added to the smooth paste to step1 to get slurry.



Pharmaceutical Suspensions

Preparation...

Step 3: the slurry is transformed to a graduated cylinder, the mortar is rinsed with successive portion of the vehicle.

Step 4:

- decide whether the solids are suspended in a structured vehicle or flocculated and then suspended
- add the vehicle containing the suspending agent/ flocculating agent
- make up the dispersion to the final volume.

WORK DONE!

Pharmaceutical Suspensions

Rheology

- An ideal pharmaceutical suspension would exhibit **thixotropic properties**
- A high apparent viscosity at low rates of shear during storage
 - To reduce sedimentation or preferably remain permanently suspended.
- At higher rates of shear (shaking) of the product to be poured easily from the container.
- For external use,
 - spread easily with out excessive rubbing
 - should not be so fluid that it runs off the skin surface.

Pharmaceutical Suspensions

Rheology...

- For injection
 - the product should pass easily through a hypodermic needle.
- In a flocculated system, it may not be sufficient to prevent rapid settling.
 - ✓ suspending agents may be used to increase the apparent viscosity of the system.
- Fluids may have:
 - Pseudoplastic
 - Plastic
 - Thixotropic behavior

Pharmaceutical Suspensions

Rheology...

- No shear during storage
- High shear is encountered when the container is shaken and the product is poured from the bottle.
- Pseudoplastic substances: tragacanth, sodium alginate, and NaCMC
- Thixotropic: bentonite
- Mixture of bentonite and CMC: shows both pseudoplastic and thixotropic characteristics.
 - ✓ Such a combination should produce an excellent suspending medium.

Pharmaceutical Suspensions

Packaging

- Pharmaceutical suspensions for oral use are generally packed in **wide** mouth container having adequate space above the liquid to ensure proper mixing.
- Generally glass and various grades of plastics are used in packaging of suspension
- Parenteral suspensions are packed in either glass ampoules or vials.



Pharmaceutical Suspensions

Labeling and Storage

Labeling:

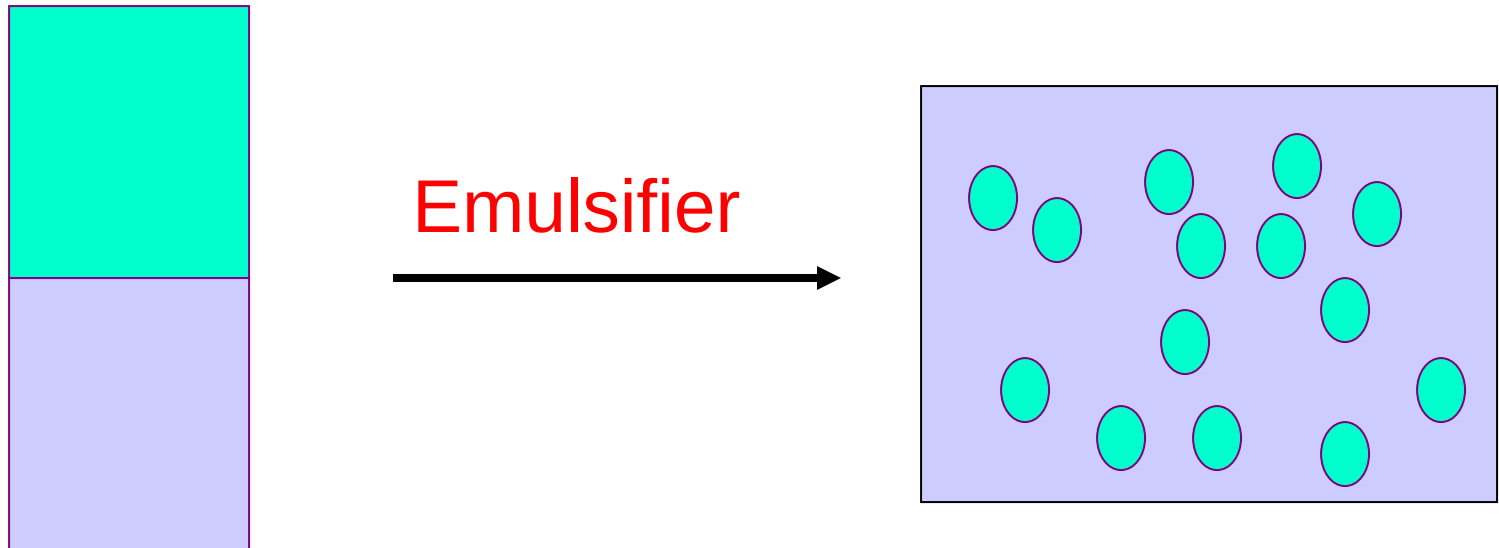
- Shake well before use
- Do not freeze
- Protect from direct light (for light sensitive drugs)
- In case of dry suspensions powder the specified amount of vehicle to be mixed may indicated clearly on label.

Storage:

- Stored at controlled temperature from 20-25 °C
- Suspensions should be stored in cool place but should not be kept in a refrigerator

Chapter 8

Pharmaceutical Emulsions



Anteneh Belayneh

(B. Pharm, MSc in Pharmaceuticals)

Pharmaceutical Emulsions

Outline

- Introduction
- Theories of emulsification
- Formulation
- Preparation of emulsion
- Emulsion type determination
- Physical instabilities
- Chemical instability
- Microbial instability
- Pharmaceutical applications

Pharmaceutical Emulsions

Introduction

- An emulsion is a dispersion in which the dispersed phase is composed of small globules of a liquid distributed throughout a vehicle in which it is immiscible.
- the dispersed phase is the *internal phase*, and
- the dispersion medium is the *external* or *continuous phase*.
- ***Oil-in-water (o/w)***: emulsions with an oleaginous internal phase and an aqueous external phase.
- ***Water-in-oil (w/o)***: emulsions with an aqueous internal phase and an oleaginous external phase.

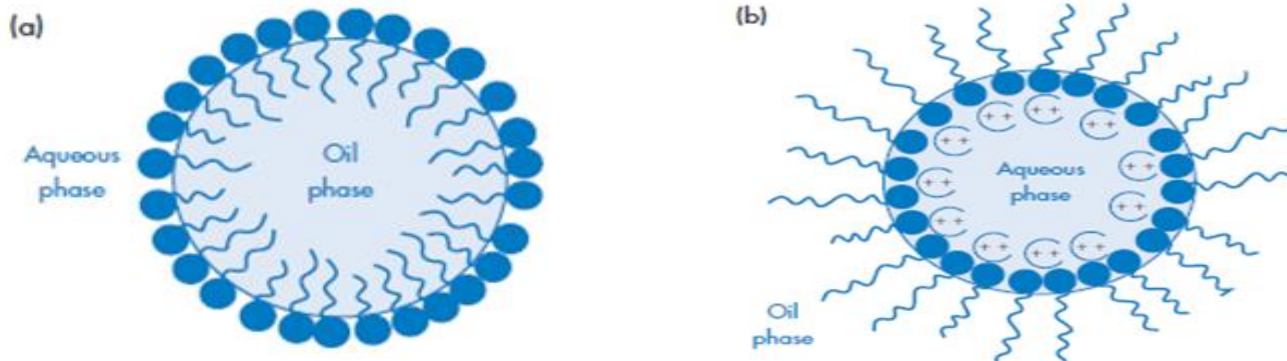
Pharmaceutical Emulsions

Introduction...

- the continuous phase is miscible with like solvents.
 - ✓ an o/w emulsion may be diluted or extended with water or an aqueous preparation, and
 - ✓ a w/o emulsion, may be diluted with an oleaginous or oil-miscible liquid.
- to prepare a stable emulsion, a third phase, an *emulsifying agent*, is necessary.
- Depending on their constituents, the viscosity of emulsions can vary greatly.
- ☞ Liquids: may be employed orally, topically, or parenterally
- ☞ Semisolids: may be applied topically (certain lotions, liniments, creams, ointments)

Pharmaceutical Emulsions

Introduction...



(a) o/w and (b) w/o emulsions

- For oral administration, o/w emulsions are used while for external use, both o/w and w/o systems can be employed.
- Semisolid emulsions are termed as creams
 - O/W creams are less greasy and are easily washable after application.
 - W/O creams are **greasy**, with **high apparent viscosity**
 - ✓ have an occlusive effect and are therefore preferred as moisturizing lotions.

Pharmaceutical Emulsions

Introduction...

- O/W emulsions are administered by all the major parenteral routes
- W/O emulsions:
 - are generally reserved for IM or SC administration where sustained release is required.
 - drug action is prolonged because the drug has to diffuse from the aqueous dispersed phase through the oil-continuous environment to reach the tissue fluids.
 - are generally of high viscosity: difficult to inject

Pharmaceutical Emulsions

Introduction...

Multiple emulsions

- are emulsions whose disperse phase contains droplets of another phase
 - an oil droplet enclosing a water droplet may be suspended in water to form a water-in-oil-in water emulsion (w/o/w)

Use:

- ✓ as delayed-action drug delivery systems (o/w/o)
- ✓ lower the viscosity of w/o emulsion (w/o/w)

Pharmaceutical Emulsions

Introduction...

Classification

- Depending on the size of the droplet:
 - Coarse emulsions: 5-20 micro meter
 - Micro emulsions: 6-100 nanometer
 - Nano emulsions: <100 nanometer

Pharmaceutical Emulsions

Advantages

- Poorly water soluble drugs may be easily incorporated with improved dissolution rates and bioavailability.
- The unpleasant taste or odor of oils can be masked partially or wholly, by emulsification.
- The absorption rate and permeation of medicaments can be controlled.
- Absorption may be enhanced by the diminished size of the internal phase.
- Formulation and technology for **organ targeted delivery** is available.
- Various particle sizes of the internal phase can be achieved by preparation technique, from micro emulsions to nanoparticles.
- Water is an inexpensive diluent and a good solvent for the many drugs and flavors that are incorporated into an emulsion.

Pharmaceutical Emulsions

Theories of emulsification

- Several theories have been proposed to explain how emulsifying agents act:
 - in producing the multi-phase dispersion, and
 - in maintaining the stability of the resulting emulsion
- The most prevalent theories:
 - surface-tension theory
 - oriented-wedge theory, and
 - interfacial film theory

Pharmaceutical Emulsions

Theories of emulsification: **Surface tension theory**

- When the liquid is in contact with a second liquid in which it is insoluble and immiscible, the force causing each liquid to resist breaking up into smaller particles is called interfacial tension.
- Substances that reduce this resistance encourage a liquid to break up into smaller drops or particles.
 - *surface-active* (surfactant) substances lower this tension

Pharmaceutical Emulsions

Theories of emulsification: **Surface tension theory...**

○ This theory assumes:

- the use of surfactants as emulsifiers and stabilizers:
 - ✓ lowers the interfacial tension of the two immiscible liquids
 - ✓ reduces the repellent force between the liquids and diminishes each liquid's attraction for its own molecules.
 - ✓ facilitate the breaking up of large globules into smaller ones, which then have a lesser tendency to reunite or coalesce.

Pharmaceutical Emulsions

Theories of emulsification: **Oriented-wedge theory**

- The theory is based on the assumption that:
 - emulsifying agents orient themselves about and within a liquid **relative to their solubility in that particular liquid**.
 - In a system containing two immiscible liquids, the emulsifying agent is **preferentially** soluble in one of the two liquids and becomes more embedded with that phase relative to the other.
 - Many surfactants have a hydrophilic portion and a lipophilic portion
 - ✓ Hence, the molecules position or orient themselves into each phase.

Pharmaceutical Emulsions

Theories of emulsification: **Oriented-wedge theory...**

- the wedge shape theory proposes that emulsifiers surround either oil globules or water globules depending on:
 - the shape and size of the molecules
 - their solubility characteristics, and,
 - thus, their orientation
- emulsifying agent, having a greater hydrophilic character than hydrophobic character, will promote **o/w** emulsions.
- **w/o** emulsions result with the use of an emulsifier that is more hydrophobic.

Pharmaceutical Emulsions

Theories of emulsification: **Interfacial film theory**

- This theory proposes that the emulsifier forms an interface between the oil and water.
 - this film surrounds the droplets of the internal phase as a thin layer of film adsorbed on the surface of the drops.
 - the film prevents the contact and coalescing of the dispersed phase;
 - ✓ the tougher and more pliable the film, the greater the stability of the emulsion.
 - Naturally, the surfactant must be available to coat the entire surface of each drop of internal phase.
- the formation of an o/w or a w/o emulsion depends on the degree of solubility of the emulsifier in the two phases
 - ✓ Similar to the oriented wedge theory,.

Pharmaceutical Emulsions

Theories of emulsification...

Which theory best explains a given emulsion?

- **None** of the emulsion theories, in reality, can individually explain the mechanism by which the many and varied emulsifiers promote emulsion formation and stability.
 - ✓ even within a given emulsion system, more than one of the theories of emulsification are applicable.
- For instance,
 - reducing the interfacial tension is critical during initial formation of an emulsion
 - but the formation of a protective wedge of molecules or film of emulsifier is equally important for continued emulsion stability.

Pharmaceutical Emulsions

Formulation

- When two immiscible liquids are mixed, shaken together or mechanically agitated both phases tend to form droplets of various sizes.
- The **surface free energy** (sum of intermolecular interaction) of the system, which is dependent on both total surface area and interfacial tension is **raised** by the increase in surface area produced during dispersion.
 - Thus, the system becomes thermodynamically unstable, which results in **coalescence** of these droplets
- If **agitation ceases**, coalescence will continue until complete phase separation, the state of minimum free energy, is reached

Pharmaceutical Emulsions

Formulation...

○ Hence, **emulsifying agents** are included to prevent coalescence of emulsion.

- Surfactants' adsorption at the oil-water interface form monomolecular films
- Presence of the surfactant monolayer at the surface of the droplet **reduces the possibility of collisions**
 - ✓ this helps to maintain the particles in a dispersed state

Pharmaceutical Emulsions

Formulation...

- Emulsifiers can be grouped into three groups:
 - 1) surface active agents
 - 2) natural (macromolecular) polymers, and
 - 3) finely divided solids.
- The choice of surfactant depends on its solubility to the phases
- In general, the phase in which the emulsifier is most soluble becomes the continuous phase
 - Hydrophilic surfactants (HLB:9-12) → o/w emulsions
 - Lipophilic surfactants (HLB:3-6) → w/o emulsions

Pharmaceutical Emulsions

Formulation...

Surface active agents

- Surfactants, or amphiphiles, reduce interfacial tension because of their adsorption at the oil-water interface to form monomolecular films.
 - the dispersed droplets are surrounded by a coherent monolayer.
 - ✓ helps prevent coalescence between two droplets as they approach one another.
 - ✓ ideally, such a film should be flexible so that it is capable of reforming rapidly if broken or disturbed.
- the presence of a surface charge, which will cause repulsion between adjacent particles, is an additional effect promoting stability.

Pharmaceutical Emulsions

Formulation...

Surface active agents...

- ***Sorbitan esters (Spans)***: are mixtures of partial esters of sorbitol and its mono- and dianhydrides with fatty acid.
- ✓ they are generally insoluble in water.
- ✓ they are used as w/o emulsifiers and as wetting agents.

Chemical name	Commercial name	HLB
Sorbitan laurate	Span 20	8.6
Sorbitan palmitate	Span 40	6.7
Sorbitan stearate	Span 60	4.7
Sorbitan tristearate	Span 65	2.1
Sorbitan oleate	Span 80	4.3
Sorbitan trioleate	Span 85	1.8

Pharmaceutical Emulsions

Formulation...

Surface active agents...

- **Polysorbates (Tweens)**: are complex mixtures of partial fatty acid esters of sorbitol and its mono- and di-anhydrides copolymerized with approximately 20 moles (usually) of ethylene oxide for each mole of sorbitol and its anhydrides.
- ✓ they are generally miscible with water.
- ✓ they are used as o/w emulsifiers.

Chemical name	Commercial name	HLB
Polyoxyethylene (20) sorbitan laurate	Polysorbate (Tween) 20	16.7
Polyoxyethylene (20) sorbitan palmitate	Polysorbate (Tween) 40	15.6
Polyoxyethylene (20) sorbitan stearate	Polysorbate (Tween) 60	14.9
Polyoxyethylene (20) sorbitan tristearate	Polysorbate (Tween) 65	10.5
Polyoxyethylene (20) sorbitan oleate	Polysorbate (Tween) 80	15
Polyoxyethylene (20) sorbitan trioleate	Polysorbate (Tween) 85	11

Pharmaceutical Emulsions

Formulation...

Surface active agents...

Required HLB

Ingredients	Required HLB for O/W	Ingredients	Required HLB for O/W	
Cottonseed oil	6–7	Carbon tetrachloride	16	
Petrolatum	8	Lauric acid	16	
Mineral oil	10-12	Oleic acid	17	
Methyl silicone	11	Ingredients emulsion	Required HLB for O/W	Required HLB for W/O
Carnauba wax	12-14			
Lauryl alcohol	14			
Castor oil	14			
Kerosene	12-14			
Cetyl alcohol	13-16			
Stearyl alcohol	15-16			
		Beeswax	9–11	5
		Paraffin wax	10	4
		Mineral oil	10–12	5–6
		Lanolin, anhydrous	12–14	8

Pharmaceutical Emulsions

Formulation...

Surface active agents...

Required HLB...

- Mixtures of surfactants with higher and lower (than required) HLB values give more stable emulsions than single surfactants.
- HLB of surfactant mixtures can be calculated as:

$$\text{HLB}_{\text{mixture}} = f\text{HLB}_A + (1 - f)\text{HLB}_B$$

Where, f is fraction of A and $(1 - f)$ is fraction of B.

E.g. calculate the proportion of Span 60 (HLB = 4.7) and Tween 80 (HLB = 15.0) required to prepare mixture surfactant with HLB value of 10.

$$\text{HLB}_{\text{mixture}} = 4.7x + (1 - x) * 15$$

$x = 0.485$ (fraction of Span 60) and $1-x = 0.515$ (fraction of Tween 80)

Pharmaceutical Emulsions

Formulation...

Surface active agents...

Required HLB...

- When more than one oils are used, Required HLB values for the emulsion can be calculated as:

$$\text{RHLB}_{\text{mix}} = \frac{W_t \text{ of oil} * \text{RHLB}}{W_{\text{all oils}}}$$

E.g. the following formula is required to prepare O/W emulsion.

Beeswax.....15g

Lanolin.....10g

Paraffin.....20g

Cetyl alcohol...5g

What should be total RHLB for this emulsion?

Ingredient	RHLB
Beeswax	$15/50 \times 9 = 2.70$
Lanolin	$10/50 \times 12 = 2.40$
Paraffin	$20/50 \times 10 = 4.00$
Cetyl alcohol	$5/50 \times 15 = 1.50$
Total RHLB	$= 10.60$

Pharmaceutical Emulsions

Formulation...

Surface active agents...

Required HLB...

How much of surfactant is sufficient?

- amount of surfactant is determined based on formulation studies.
- But, the minimum amount of surfactant mixture (Q_s) can be estimated as:

$$Q_s = \frac{6\left(\frac{\rho_s}{\rho}\right)}{10 - 0.5RHLB} + \frac{4Q}{10000}$$

Where, ρ_s is the density of the surfactant mixture, ρ is the density of the dispersed phase, and Q is the percentage of the continuous phase of the emulsion.

Pharmaceutical Emulsions

Formulation...

Natural (Macromolecular) polymers

- Multimolecular adsorption and film formation
 - Hydrated lyophilic colloids:
 - ✓ can be regarded as surface active, but they differ from synthetic surfactant.
 - they do not cause an appreciable lowering of interfacial tension, and
 - they form a multi-rather than a monomolecular film at the interface.
 - their action as emulsifying agents is due mainly to the latter effect because the films thus formed are strong and resist coalescence.
 - ✓ the significant increase in the viscosity of the dispersion medium could also improve stability.

Pharmaceutical Emulsions

Formulation...

Solid particle adsorption

- Finely powdered solid particles which are wetted to some degree by both oil and water can act as emulsifying agents.
 - ✓ this results from their being concentrated at the interface, where they produce a particulate film around the dispersed droplets so as to prevent coalescence.
- Powders that are wetted preferentially by water form o/w emulsion, whereas those more easily wetted by oil form w/o emulsions.

Pharmaceutical Emulsions

Formulation...

Table: Emulsifying agents derived from natural products and finely divided solids

Class	Example
Polysaccharide	Acacia Carageen Methylcellulose
Protein	Gelatin
Glycoside	Saponin
Phospholipid	Lecithin
Sterol	Wool fat Cholesterol and its esters
Finely divided solids	Bentonite Veegum Aluminium hydroxide

Pharmaceutical Emulsions

Formulation...

Other ingredients

- **Antioxidants:** butylated hydroxy toluene (BHT) and butylated hydroxyanisole (BHA)
- **Humectants:** propylene glycol, glycerol, and sorbitol are often added to dermatological preparations
- **Preservatives:** benzoic acid, parahydroxybenzoic acid esters, phenoxyethanol, Chloroform Water
 - **W/O** emulsions are less susceptible to attack than **O/W** emulsions
 - ✓ because the aqueous continuous external phase can produce ideal conditions for the growth of bacteria, moulds and fungi.

Pharmaceutical Emulsions

Formulation...

*Other ingredients: **Preservatives***

- Bacteria can degrade nonionic and anionic emulsifying agents, glycerin, vegetable gums (as thickeners).
 - this results in phase separation, gas and odor formation, discoloration, changes in rheological properties
- Two phase system: adequate concentration of preservative should be available in water phase as bacteria mainly grow in aqueous phase
- ✓ Therefore, preservative should:
 - strongly partition in favor of water
 - be in its un-ionized form to penetrate bacterial membrane
 - not be bound to other components of the emulsion

Pharmaceutical Emulsions

Preparation methods

- Emulsions may be prepared in different methods
- **Small scale**
 - a mortar and pestle, a mechanical blender, a homogenizer.
 - three main methods of *Emulsion Preparation*
 1. **Continental or dry gum method**
 2. **English or wet gum method**
 3. **Bottle method**
- **Large scale**
 - Colloid mills, high-pressure homogenizers, microfluidizers, ultrasonic homogenizers may be used to prepare an emulsion.

Pharmaceutical Emulsions

Preparation methods: **Dry gum method**

- is also referred to as the **4:2:1 (O:W:G)** or continental method
 - ✓ Oil - 4 parts by volume
 - ✓ Aqueous phase - 2 parts by volume
 - ✓ Gum - 1 part by weight
- The preparation of an emulsion has two main components:
 - Preparation of a concentrate called the ‘**primary emulsion**’.
 - Dilution of the concentrate.
- The proportions are important when making the primary emulsion, to prevent the emulsion breaking down on dilution or storage.
- NB: 4:2:1 is used for **fixed oils** while 3:2:1 for mineral oils

Pharmaceutical Emulsions

Preparation methods: **Dry gum method...**

E.g What quantities of oil, water, and gum would be required to produce 100 mL of a 20% emulsion of a fixed oil?

○ For a 20% emulsion 20mL of the oil in 100mL of emulsion would be required.

- 4 parts would be equivalent to 20mL of oil.
- 2 parts would be equivalent to 10mL aqueous phase.
- 1 part would be equivalent to 5 g of gum.

○ The formula for the primary emulsion would therefore be:

Fixed oil 20 mL

Aqueous phase 10 mL

Gum 5 g

Pharmaceutical Emulsions

Preparation methods: **Dry gum method...**

E.g. What quantities of oil, water, and gum would be required to produce 200 mL of 30% v/v Cod liver oil emulsion?

- 60mL of Cod Liver Oil BP is required, therefore 4 parts 60mL.
 - Two parts would be equivalent to 30 ml aqueous phase.
 - 1 part would be equivalent to 15 g of gum
- The formula for the primary emulsion would therefore be:
- | | |
|--------------------|-------|
| Cod Liver oil | 60 mL |
| Aqueous phase | 30 mL |
| Gum | 15 g |

Pharmaceutical Emulsions

Preparation methods: **Dry gum method...**

Procedure

1. The acacia or O/W emulsifier is triturated with the oil in a dry mortar, until uniformly mixed.
2. The two parts of water are added all at once.
 - Then the mixture is triturated immediately, rapidly and continuously until the primary emulsion is formed (~3 min)
 - ✓ the end point of the preparation could be noticed when a **creamy white** and crackling sound or 'clicking' sound is observed.

Pharmaceutical Emulsions

Preparation methods: **Dry gum method...**

Procedure...

3. Other liquid ingredients that are soluble in the external phase may then be added.
4. Solid substances such as active ingredient, preservatives, colorants, and flavoring agent usually dissolved in water then added to an emulsion.
5. Any substance which might reduce the physical stability of the emulsion, such as alcohol (which may precipitate the gum) should be added as near to the end of the process as possible to avoid breaking the emulsion.
6. Finally make up to final volume with water

Pharmaceutical Emulsions

Preparation methods: **Wet gum method**

- also called English method
- the same proportion of water, gum and oil is used but the process is different.
- more difficult to use, but produces a more stable product.
- produces O/W emulsion.

Pharmaceutical Emulsions

Preparation methods: **Wet gum method...**

Steps:

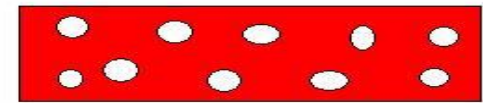
1. Triturating of *acacia with water in a mortar*.
2. The *oil is added slowly* in portions, triturating continuously.
3. The mixture is triturated for several minutes to form the primary emulsion.
4. Additional water can be added after the primary emulsion is prepared
5. Other substances may be added.
6. Finally make up to final volume with water.

Pharmaceutical Emulsions

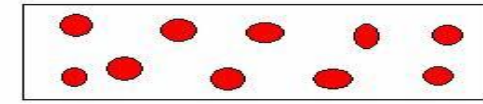
Preparation methods: **Bottle method**

- Another variant of the Continental Method
 - it is used for ***volatile oils*** or ***oleaginous substances of low viscosity***.
1. The powder acacia is placed in a dry bottle.
 2. **Two** parts of oil is then added.
 3. The bottle is then capped and shaken.
 4. Water (equal volume with oil) is then added immediately in portions, and shaken until primary emulsion is formed.
 6. Additional water can be added after the primary emulsion is prepared.
 5. The other ingredients are added.
 6. Finally QS with water to final volume.

Pharmaceutical Emulsions



O/W Emulsion



W/O Emulsion

Emulsion type determination

○ Dye (staining) test

- A small quantity of a water soluble dye such as methylene blue or amaranth (red) may be dusted on the surface of the emulsion

- ✓ o/w emulsion: the dye will dissolve throughout the water.

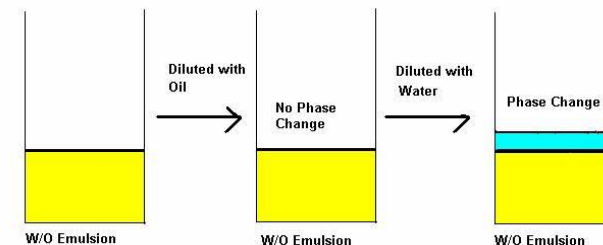
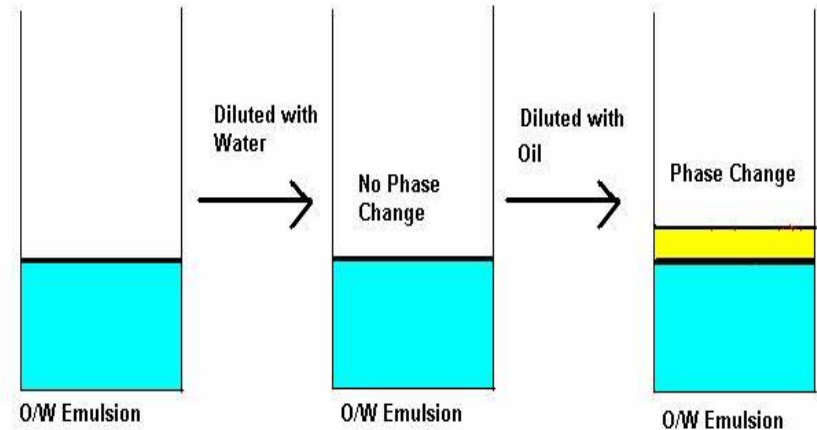
- ✓ w/o emulsion: the particles of dye will remain on the surface

○ Dilution (miscibility) test:

- dilution of the emulsion with water

- ✓ o/w emulsion: the emulsion mixes freely with water

- ✓ w/o emulsion: is miscible with oil



Pharmaceutical Emulsions

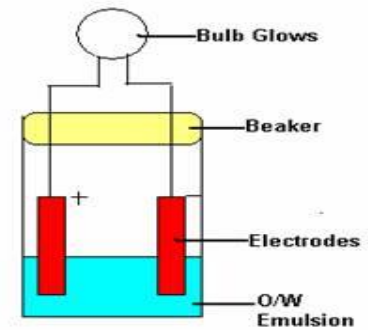
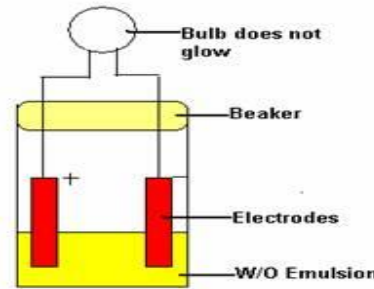
Emulsion type determination.

○ Conductivity:

- a pair of electrodes connected to an external electric source and immersed in the emulsion.
 - ✓ o/w emulsion: a current will pass through the emulsion and can be made to deflect a voltmeter needle or cause a light in the circuit to glow.
 - ✓ w/o emulsion: the emulsion fails to transmit the current.

○ Fluorescence:

- When oils are exposed to UV rays, they fluoresce.
 - ✓ o/w emulsion exhibit spotty pattern and w/o emulsion fluoresce throughout the field.



Pharmaceutical Emulsions

Emulsion type determination...

- Direction of creaming:

- As oils are lower in density than water:

- ✓ w/o: droplets will sediment

- ✓ o/w: there will be upward movement/creaming.

Pharmaceutical Emulsions

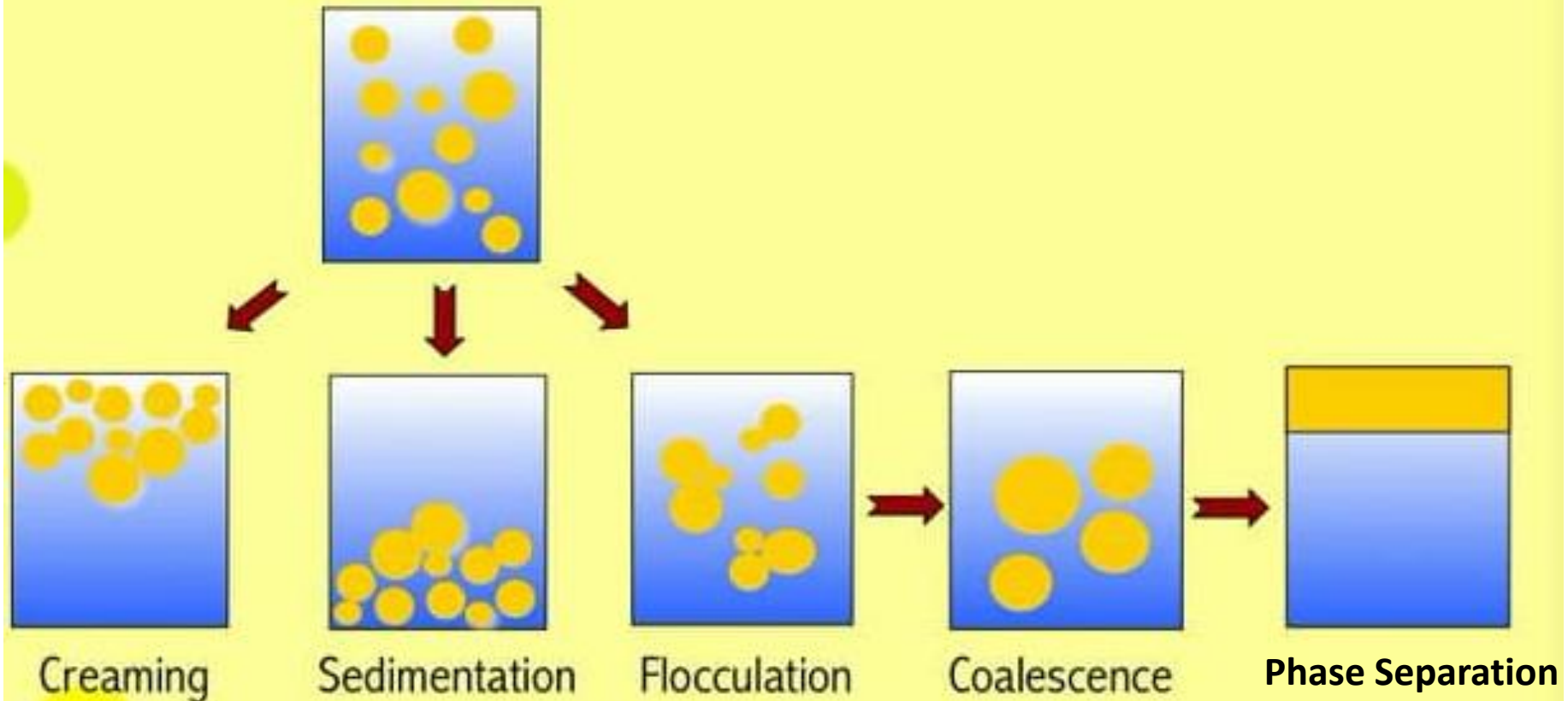
Physical instability

- A stable emulsion may be defined as a system in which the globules:
 - ✓ *retain their initial character*
 - ✓ *remain uniformly distributed throughout the continuous phase*
- Different instability problems
 - Reversible: such as creaming, sedimentation, and flocculation
 - Irreversible: such as coalescence and cracking

Pharmaceutical Emulsions

Physical instability...

Mechanisms of Emulsion Instability



Pharmaceutical Emulsions

Physical instability: **Creaming**

- The disperse phase, according to its **density** relative to that of the continuous phase
 - ✓ rises to the top, or
 - ✓ sinks to the bottom of the emulsion, forming a layer of more concentrated emulsion.
- **Upward creaming**: ρ dispersed phase $<$ ρ continuous phase (o/w emulsion), the velocity of the sedimentation becomes negative.
- **Downward creaming**: ρ dispersed phase $>$ ρ continuous phase (w/o emulsion), the velocity of the sedimentation becomes positive.

Pharmaceutical Emulsions

Physical instability: **Creaming...**

- **The rate of creaming can be increased** if
 - ✓ the density difference is greater
 - ✓ force of gravity is increased through centrifugation
 - ✓ diameter of the globule is increased
- Creaming is undesirable from a pharmaceutical point of view:
 - Creamed emulsion is **inelegant** in appearance
 - Possibility of **inaccurate dosage**
 - Increases the **likelihood of coalescence** as the globules are close together in the cream

Pharmaceutical Emulsions

Physical instability: **Creaming...**

- Creaming is governed by Stock's law.
- Rate of sedimentation will be decreased by:
 - reduction in the globule size (e.g. by homogenizing the emulsion)
 - increasing viscosity of continuous phase (e.g. by using thickening agents such as tragacanth or methyl cellulose)
 - decreasing the density difference between the two phases

Pharmaceutical Emulsions

Physical instability: **Flocculation**

- A ***weak reversible*** association between emulsion globules separated by thin films of continuous phase.
 - the individual droplets retain their separate identities, but each floccule or cluster of droplets behaves physically as a single unit.
 - the association arises from the interaction of attractive and repulsive forces between droplets.
 - the cream floccules can be redispersed easily, and a uniform mixture is reconstituted from a creamed emulsion by agitation.
 - ✓ b/c the oil globules are still surrounded by a protective sheath of emulsifying agent.

Pharmaceutical Emulsions

Physical instability: **Coalescence and Breaking**

- Coalescence: is the fusion of the droplets, leading to a decrease in their numbers.
 - ✓ i.e. where dispersed phase droplets merge to form larger droplets.
 - ✓ this may lead to phase separation (breaking or cracking).
- Breaking: the disperse phase coalesces and forms a separate layer.
 - re-dispersion cannot be achieved by shaking and the preparation is no longer an emulsion.
- Factors:
 - ✓ relative magnitude of forces between droplets
 - ✓ disruption of interface
 - ✓ dehydration, freezing

Pharmaceutical Emulsions

Physical instability: **Coalescence and Breaking...**

○ Cracking can occur:

- if the oil turns rancid during storage.
- by addition of a chemical that is incompatible with the emulsifying agent, thus destroying its emulsifying ability.

Eg. Surfactants of opposite ionic charge, (e.g. addition of cetrimide (cationic) to an emulsion stabilized with sodium oleate (anionic))

○ Strategies to reduce coalescence and breaking

- ✓ adding thickening or gelling agent
- ✓ increasing thickness of interface
- ✓ increasing repulsion or reduce attraction

Pharmaceutical Emulsions

Physical instability...

Bacterial growth: protein materials and non-ionic surfactants are excellent media for bacterial growth.

Temperature change:

- rise in temperature:
 - ✓ protein emulsifying agents may be denatured, and
 - ✓ the solubility characteristics of non-ionic emulsifying agents change
- Freezing: ice formed disrupt the interfacial film around the droplets

Pharmaceutical Emulsions

Physical instability: **Phase inversion**

- it refers to the process whereby there will be an exchange between the disperse phase and the dispersion medium.
 - ✓ For example, an O/W emulsion may with time or change of conditions invert to a W/O emulsion

Causes

- **Coalescence:** results in the formation of progressively larger droplet which leads to phase separation
- **Factors that affect the HLB of the system**
Eg. temperature and/or electrolyte concentration

Pharmaceutical Emulsions

Physical instability: **Phase inversion...**

Causes...

○ **Volume fraction of the disperse phase**

- For stability of an emulsion, the optimum range of concentration of dispersed phase is 30–60% of the total volume.
- As the concentration of the disperse phase approaches a theoretical maximum of 74% of the total volume, phase inversion is more likely to occur.

○ **Addition of electrolyte**

- Addition of CaCl_2 into o/w emulsion formed by sodium stearate can be inverted to w/o emulsion.
 - ✓ because calcium stearate is formed.

Pharmaceutical Emulsions

Chemical instability

- Ingredients should be chemically compatible
- Ionic emulsifiers are usually incompatible with materials of opposite charge
- Precipitation of emulsifiers: by the addition of material in which they are insoluble
- Changes in pH: breaking of emulsion
- Many of the oils and fats are susceptible to oxidation

Pharmaceutical Emulsions

Microbial instability

- Growth of MO: is supported by the water component
 - Contamination affects the physicochemical properties
 - Gas production
 - Color and odor change
 - Hydrolysis of fats and oils
 - pH changes in the aqueous phase
 - Breaking of emulsions
- ✓ Preservative is a must

Pharmaceutical Emulsions

Microbial instability...

- Desirable features of a preservative
 - A wide spectrum of activity: all bacteria, yeast and moulds
 - Bactericidal rather than bacteriostatic activity
 - Free from toxicity, irritation or sensitization activity
 - High water solubility, low oil/water partition coefficient
 - Compatible with other ingredients
 - Stable and effective over a wide range of pH and temperature
- Benzoic acid, sorbic acid, chlorocresol, methyl paraben and propyl paraben

Pharmaceutical Emulsions

Pharmaceutical applications

- To mask disgusting taste of certain medicinal agents
 - o/w: palatable administration of distasteful oil.
- Reduced size of the oil: more digestible and readily absorbed
 - Liquid drug in the form of minute globules
- To control the absorption rate of drug like depot-preparations.
- To prepare liquid formulation involving two or more medication/food in oil phase & aqueous phases (TPN).
- For parenteral administration
- Emulsions to be applied externally may be prepared as o/w or w/o depending on factors as
 - the nature of therapeutic agents to be incorporated
 - the desirability of emollient effect, and the condition of the skin.



PHARMACIST